The Rate of Structural Change: The Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study

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• PURPOSE: To compare rates of topographic change in ocular hypertensive eyes that develop primary open-angle glaucoma (POAG) compared to eyes that do not, and to identify factors that influence the rate of change.

• DESIGN: Longitudinal, randomized clinical trial.

• METHODS: Four hundred forty-one participants (832 eyes) in the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study were included. POAG was defined as repeatable visual field, photography-based optic disc changes, or both. The rate of topographic change in the 52 participants (66 eyes) who developed POAG was compared with that of participants who did not develop POAG using multivariable mixed effects models.

• RESULTS: In both univariate and multivariate analyses, the rate of rim area loss was significantly faster in eyes in which POAG developed than in eyes in which it did not (univariate mean, -0.0131 mm^2/year and -0.0026 mm^2/year, respectively). The significantly faster rate of rim area loss in black persons found in the univariate analysis did not remain significant when baseline disc area was included in the model. In multivariate analyses, the rate of rim area loss and other topographic parameters also was significantly faster in eyes with worse baseline visual field pattern standard deviation and higher intraocular pressure during follow-up. Moreover, a significant rate of rim area loss was detected in eyes in which POAG did not develop ($P < .0001$). The rate of rim area loss in eyes with an optic disc POAG endpoint was significantly faster than in those with a visual field POAG endpoint.

• CONCLUSIONS: The rate of rim area loss is approximately 5 times faster in eyes in which POAG developed compared with eyes in which it did not. These results suggest that measuring the rate of structural change can provide important information for the clinical management of ocular hypertensive patients. Additional follow-up is needed to determine whether the statistically significant change in the eyes in which POAG did not develop represents normal aging or glaucomatous change not detected by conventional methods. (Am J Ophthalmol 2013;155:971–982. © 2013 by Elsevier Inc. All rights reserved.)

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DETECTION OF GLAUCOMATOUS CHANGE IS ONE of the most challenging aspects of the clinical assessment of ocular hypertensive and glaucoma patients. The ability to differentiate between eyes that are progressing rapidly and eyes that are progressing slowly is important for the appropriate management of patients with glaucoma. Patients with rapidly progressing glaucoma may require adjustments to the treatment regimen to prevent the development of significant visual impairment, depending on their age and life expectancy. Alternatively, patients with slowly progressing disease may require less aggressive treatment when significant visual dysfunction is not expected in their lifetimes.

New image analysis techniques have improved our ability to identify structural change and, most importantly, to measure the rate of optic disc and retinal nerve fiber layer changes. Although imaging instruments have been available for almost 20 years, there is a paucity of information on the rate of structural change in patients with ocular hypertension.[1–5] Because glaucoma is a slowly progressing disease that occurs in a relatively small proportion of ocular hypertensive patients, studies investigating structural change over time in ocular hypertensive patients require

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extensive follow-up and a large population. The Confocal Scanning Laser Ophthalmoscopy (CSLO) Ancillary Study to the Ocular Hypertensive Treatment Study (OHTS) was initiated in 1995 with annual CSLO imaging through 2009 to provide the long-term follow-up necessary to characterize structural change over time in ocular hypertensive patients.[6–9] The purpose of the present study was to compare rates of change in topographic optic disc parameters in eyes in which primary open-angle glaucoma (POAG) developed with those eyes in which POAG did not develop and to evaluate factors that influence the rate of structural change.

METHODS

PARTICIPANTS INCLUDED IN THIS REPORT MET THE OHTS inclusion and exclusion criteria[10] and participated in the CSLO Ancillary Study to the OHTS with at least 1 good-quality Heidelberg Retina Tomograph image during follow-up. Seven OHTS clinics participated in the CSLO Ancillary Study to the OHTS: Hamilton Glaucoma Center, University of California, San Diego, California; New York Eye and Ear Infirmary, New York, New York; Devers Eye Institute, Portland, Oregon; Henry Ford Medical Center, Troy, Michigan; Jules Stein Eye Institute, University of California, Los Angeles, Los Angeles, California; University of California, Davis, Davis, California; and Scheie Eye Institute, University of Pennsylvania, Philadelphia, Pennsylvania. The OHTS clinical trial registration number (ClinicalTrials.gov) is NCT00000125. The CSLO ancillary study to the OHTS was conducted in compliance with the institutional review board requirements at each study center and the Health Insurance Portability and Accountability Act. Written informed consent for participation in this ancillary study was obtained from all participants before enrollment.

OHTS eligibility criteria required participants to have an intraocular pressure (IOP) ranging from 24 to 32 mm Hg in at least 1 eye and from 21 to 32 mm Hg in the fellow eye, as well as 2 normal, reliable automated achromatic 30-2 full threshold visual fields (Carl-Zeiss-Meditec, Dublin, California, USA) together with normal-appearing optic discs based on clinical examination and review of stereoscopic optic disc photographs.[10] The optic disc reading center graders assessed photographs and estimated horizontal and vertical cup-to-disc ratios by contour.

The development of POAG, the primary endpoint for OHTS, was defined as a confirmed visual field abnormality or a confirmed clinically significant stereophotograph-based optic disc deterioration attributed to POAG by a masked endpoint committee.[10] Specifically, the endpoint committee reviewed all confirmed visual field abnormalities and confirmed disc progression to determine whether the change was most probably the result of POAG, most probably not the result of POAG, or, in the case of disc progression, whether the progression was not clinically significant or an artifact. Endpoint committee members, masked as to treatment history, reviewed baseline and follow-up case report forms, visual fields, and stereoscopic disc photographs of both eyes. The first date of 3 consecutive abnormal visual fields or the first date of 2 consecutive sets of stereophotographs that classified the eye as reaching a POAG endpoint was used as the date for a POAG endpoint in all analyses.

As described previously,[6–9] 3 10-degree images were obtained from both eyes and 3 15-degree Heidelberg Retina Tomograph (HRT; Heidelberg Engineering GmbH, Heidelberg, Germany) images were obtained from the right eye at the annual OHTS dilated fundus examination. If both 10-degree and 15-degree good-quality images were available, the 10-degree images were used in this analysis. The scans were obtained using the HRT 1 classic instrument throughout the study and were analyzed using software version 3.0. Corneal curvature measurements were used to correct images for magnification error. Corrective lenses were used during image acquisition when astigmatism was more than 1 diopter. The mean of 3 images was used for statistical analyses. As described previously, the CSLO Reading Center at the University of California, San Diego, conducted all quality assessment and image processing and certified all operators at every site according to standard protocols.[9] In brief, CSLO Reading Center staff reviewed each image series (images at 32 consecutive focal planes) for clarity, appropriate focus and depth adjustment, and minimal eye movement. In addition, each mean topography image was monitored for adequate reproducibility (standard deviation of the mean image, <50 μm). Of a total of 7556 right and left eye testing sessions, data for 461 (6.1%) sessions were excluded from the analysis because of poor-quality images.

Because the CSLO Ancillary Study to the OHTS was funded after the initiation of enrollment in OHTS, 77% of participants completed their first CSLO examination visit after their OHTS baseline randomization visit.[6,7] For this reason, 7 participants with documented optic disc deterioration or visual field abnormality that subsequently was confirmed and attributed to POAG at or before their first CSLO imaging session were excluded from the analysis. The current report includes all good-quality images from the first CSLO visit to the closure date for the OHTS (March 2009) or to the first suspicious date of POAG, whichever was first.

The rate of topographic change was measured using the following CSLO stereometric parameters: rim area and volume, cup area and volume, rim-to-disc area ratio, mean cup depth, retinal nerve fiber layer (RNFL) thickness and cross-sectional area, and cup shape. Contour lines outlining the disc margin of the baseline image, necessary for calculating stereometric parameters, were drawn by certified operators at the University of California,